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Number 65 24 Apr 1947

SYNTHESIS OF EMETINE

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SYNTHESIS OF EMETINE

COUNTRY : Japan

ORIGIN : Japanese Research Reports

SOURCE : Periodical "Proceedings of the Imperial Academy"

DATE OF INFORMATION: Jun 1940, Dec 1941, Jun 1941

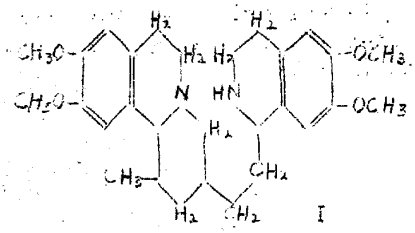
53. Studies on the Synthesis of Emetine and its Analogues (Preliminary Report). The Oxidation of N-B-Phenethyl-3-carbalkoxy-pyridinium-Salt.

By Shigehiko SUGASAWA, Kiiti SAKURAI and Toshirō OKAYAMA, Pharmaceutical Institute, Tokyo Imperial University.

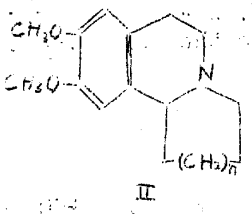
(Comm. by Y. ASAHINA, M.I.A., June 12, 1940)

In connection with the syntheses of dibenzopyridocolines,[1] the present authors have for some time been engaged with the synthesis of emetine and its analogues, since according to Brindley and Pyman[2] this alkaloid is a complicated derivative of benzopyridocoline as shown by the formula (I).[3]

In their previous communication Sugasawa, Sakurai and Sugimoto[4] described the synthesis of some 1,2-polymethylenetetra hydro-isoquinolines (II), therefore derivatives of pyridocoline-moiety of this alkaloid, but they were unable to develop the synthesis further and the work along this line was abandoned.



I



II

The oxidation of N-B-phenethyl-3-carbalkoxy-pyridinium-salt (III) by means of alcaline potassium ferricyanide was now investigated, because N-B-phenethyl-2-pyridone-5-carboxylic acid (IV), which is to be expected as a oxidation-product, seems, if appropriately subsituted, to offer a suitable intermediate for further synthesis. As a matter of fact the oxidation proceeded quite smoothly giving a unique acidic substance in excellent yield, which was proved to be N-B-phenethyl-2-pyridone-5-carboxylic acid (IV) by independent synthesis and the alternate (IV′) was not found in the oxidation-product in the least amount.

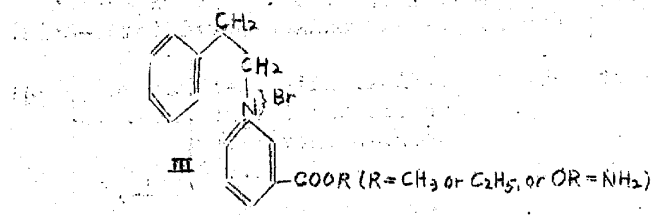
---

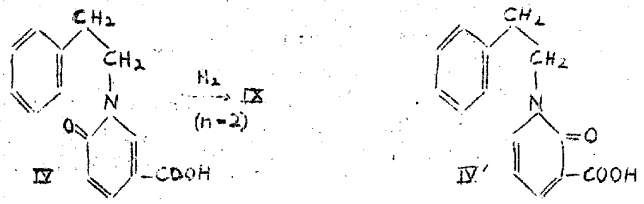
1) Sugasawa and Kakemi: (I). Proc. 14 (1938), 214, Ber. 71 (1938), 1860; (II). Proc. 15 (1939), 52, Ber. 72 (1939), 980; (III). Proc. 15 (1939), 223.

2) Soc. 1927, 1067 and previous papers.

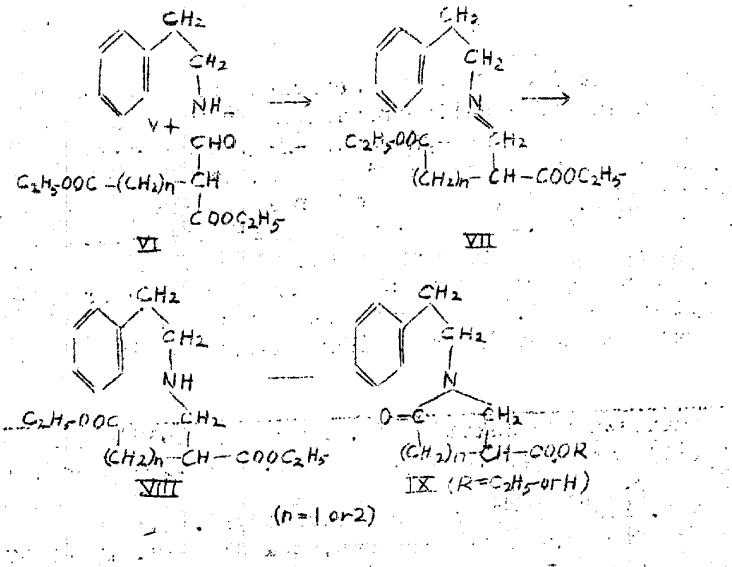
3) For further references see, Staub: Helv. 10 (1927), 826; Spath and Leithe: Ber. 60 (1927), 688.

4) Proc. 15 (1939), 82.





The synthesis of N-B-phenethyl-2-piperidone-5-carboxylic acid (IX: R = H, n = 2), the reduction-product of (IV) was carried out according to the following scheme (n = 2):-



As the preliminary to the projected synthesis the more easily accessible diethyl formylsuccinate (VI: n = 1) was substituted for diethyl formylglutarate (VI: n = 2). On standing at room temperature B-phenethylamine (V) and diethyl formylsuccinate readily enter into reaction under slight evolution of heat and separation of water. After left standing over night the bordeaux-red-coloured reaction-product was dissolved in alchol containing a few drops of acetic acid and was reduced catalytically over Adams-platin. On evaporating the solvent from the reduction-product spontaneous ring-closure ensued with a loss of alcohol giving ethyl N-B-phenethyl-2-pyrrolidone-4-carboxylate (IX: R = C_2H_5, n = 1) as viscous oil, which was hydrolysed yielding the corresponding free acid (IX: R = H, n = 1) as colourless needles of m.p. 190-191° from dil. methanol.

B-Phenethylamine (V) and diethyl formylglutarate (VI: n = 2) reacted in quite the same manner and here again the ultimate N-B-phenethyl-2-piperidone-5-carboxylic acid (IX: R = H, n = 2) was obtained without isolating the intermediates (VII: n = 2) and (VIII: n = 2). The acid forms colourless rhombic pillars of m.p. 140-141° from benzene and was proved to be identical with the acid from different origin by direct comparison.

In case homoveratryl amine and diethyl a-methyl-a'-formylglutarate could be used in the above synthesis with the same effect, ethyl N-B-(3', 4'-dimethoxyphenethyl)-3-methyl-2-piperidone-5-carboxylate, which is to be expected as the final reaction-product, would seem likely to offer a suitable intermediate for the preparation of emetine-type of compounds and the work along this line is now under progress.

The method of preparation and properties of new compounds obtained during the course of present work will be described briefly:—

(1) B-B-Phenethyl-3-carbmethoxy-pyridinium bromide (III: R = CH_3). From B-phenethylbromide and methyl nicotinate in xylene. Hexagonal plates of d.p. 197° from alcohol. ($C_{15}H_{16}O_2NBr$ requires C 55.9, H 5.0, N 4.35; Found C 55.55, H 5.0, N 3.9).

(2) N-B-Phenethyl-3-carbethoxy-pyridinium bromide (III: R = C_2H_5). From B-phenethylbromide and ethyl nicotinate as above. Colourless needles from pure alcohol, m.p. 193-194°. ($C_{16}H_{18}O_2NBr$ requires Br 23.9; Found Br 23.85).

(3) N-B-Phenethylpyridinium-bromide-3-carbonamide (III: OR = NH_2). From B-phenethylbromide and nicotinic acid amide as above. Colourless pillars from methanol-ether, m.p. 209°. ($C_{14}H_{15}ON_2Br$ requires C 51.6, H 5.2, N 8.6; Found C 51.3, H 5.1, N 8.6).

(4) N-B-Phenethyl-2-pyridone-5-carboxylic acid (IV). The oxidation of the foregoing pyridinium bromides by means of alcaline potassium ferricyanide proceeds with the simultaneous hydrolysis of

ester and amido-groups, giving N-B-phenethyl-2-pyridone-5-carboxylic acid (IV) as the sole oxidation-product. Yield over 90% of the theoretical. It forms colourless needles from dilute methanol, m.p. 190-191°. ($C_{14}H_{13}O_3N$ requires C 69.1, H 5.35, N 5.8; Found C 68.7, H 5.15 N 5.8).

(5) N-B-Phenethyl-2-piperidone-5-carboxylic acid (IX: R = H, n = 2). The foregoing acid was reduced either by means of Na-amalgam or catalytically, the former method gave better result. Colourless rhombic pillars from benzene, m.p. 140°, which was not depressed when admixed with the synthetic acid.

(6) N-B-Phenethyl-2-pyrrolidone-4-carboxylic acid (IX: R = H, n = 1). B-Phenethylamine and diethyl formylsuccinate were admixed in aequimolecular quantities and the whole was kept over night at room temperature. The bordeaux-red viscous product was dissolved in alcohol and was reduced catalytically. While the solvent being evaporated from the reduction-product spontaneous ring-closure took place with the loss of alcohol, giving ethyl N-B-phenethyl-2-pyrrolidone-4-carboxylate as yellowich viscous oil, which distilled over at 170-180° and 4 mm. The corresponding acid was obtained as colourless prisms of m.p. 192-193° from alcohol. ($C_{13}H_{15}O_3N$ requires C 66.95, H 6.4; Found C 66.6, H 6.2).

(7) N-B-Phenethyl-2-piperidone-5-carboxylic acid (IX: R = H, n = 2). From B-phenethylamine and diethyl formylglutarate as above. The ethyl ester (IX: R = C_2H_5, n = 2) forms viscous oily substance and was not induced to crystallize, but the corresponding free acid (IX: R = H, n = 2) was obtained as colourless pillars of m.p. 140° from benzene. The melting point was not depressed when admixed with the acid prepared by oxidation-method. ($C_{15}H_{15}O_3N$ requires C 68.0, H 6.9, N 5.7; Found C 68.0, H 6.9, N 5.75).

The authors are indebted to the Toshogu Memorial Fund for research grants.

All analyses were executed by Miss K. Serikawa and Miss T. Idezawa.

106. Studies on the Synthesis of Emetine and its Analogues (III).

A Synthesis of rac-C-nor-Emetine (Pyman)*).

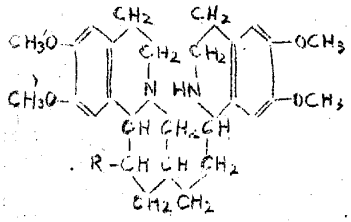
By Shigehiko SUGASAWA and Kiiti SAKURAI.

Pharmaceutical Institute, Tokyo Imperial University.

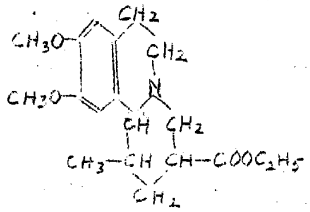
(Comm. by Y. ASAHINA, M.I.A., Dec. 12, 1941).

In the second paper[1]) of this series we described the synthesis of 4′,5′-dimethoxy-8-methyl-6-carbethoxy-3,4,5,6,7,8-hexahydro-(1′,2′: 1,2-benzochinolizine) (III) as a possible intermediate for the synthesis of rac-emetine (Pyman) (I). But the difficulty in preparing this substance (III) in quantity made us abandon to continue working along the projected scheme.

After numbers of fruitless attempts we now managed to synthesize rac-C-nor-emetine (Pyman) (II), with which preparation the present communication deals.



I: R=CH_3
II: R=H



III

Di-ethyl γ,γ-dicarbethoxy-pimelate (IV: R = C_2H_5) was prepared by the known method. When this ester was hydrolysed with the calculated amount of caustic soda in alcohol only two carbethoxy-groups on both ends were hydrolyzed, giving the corresponding γ,γ-dicarbethoxypimelic acid (IV : R = H) in good yield. On the other hand di-benzyl-γ,γ-dicarbethxy-pimelate (IV: R = $CH_2 \cdot C_6H_5$) was prepared, which on catalytic hydrogenation gave an acid, which was proved to be identical with the one prepared above. Thus the constitution of this acid (IV: R = H) prepared by the first method was fully supported.

---

*) S. Sugasawa: XXVI. Comm. upon "Studies on the Synthesis of Nitrogen-Ring-Compounds."

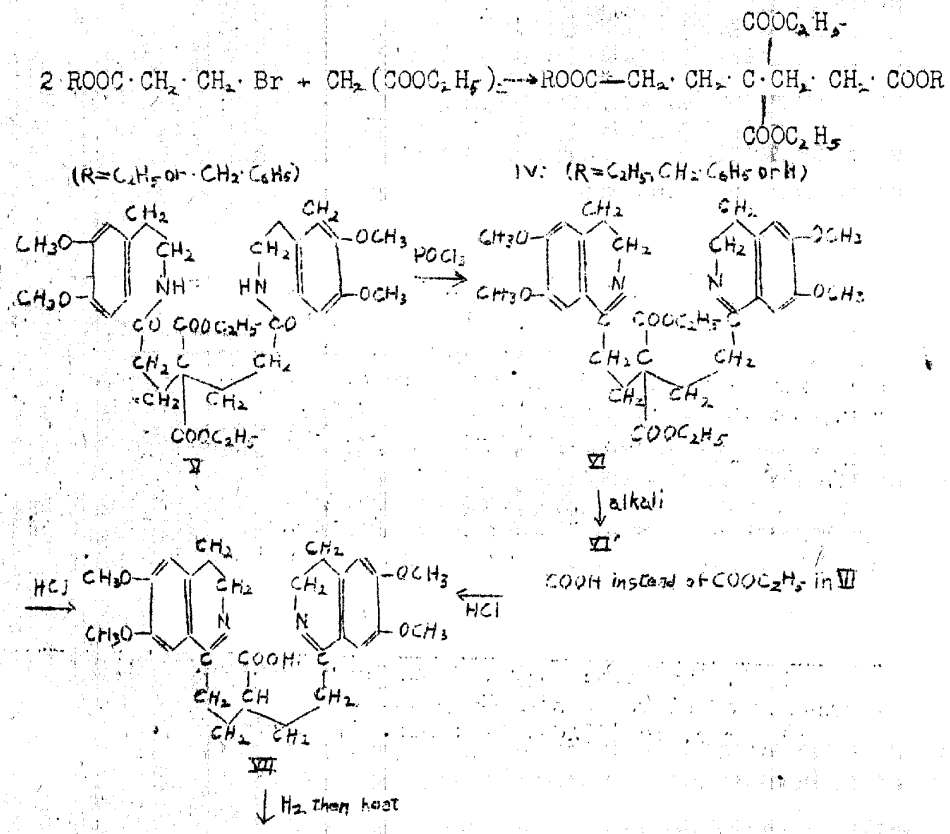
1) Proc. 16 (1940), 225; Ber. 74 (1941), 537.

Di-chloride of this acid was condensed with homoveratryl amine to yield γ,γ-dicarbethoxy pimelic acid-bis-B-homoveratrylamid (V), which on ringclosure gave diethyl a,ε-bis-(6,7-dimethoxy-3,4-dihydroisoquinolyl-1)-pentane-γ,γ-dicarboxylate (VI). The later was then boiled with an excess of hydrochloric acid until the evolution of carbondioxide had ceased, and the solution obtained was evaporated in vac. to dryness, and a,ε-bis-(6,7-dimethoxy-3,4-dihydroisoquinoly-1)-pentane-γ-carboxylic acid (VII) was isolated as dihydrochloride.

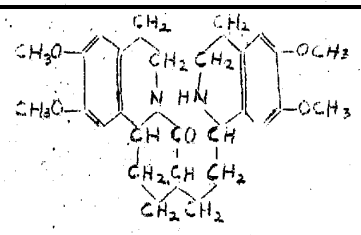
This acid was now reduced catalytically and the reduction product was worked up as usual. During this treatment H_2O was removed by heat and the corresponding lactam, therefore, 4',5'-dimethoxy-5-keto-6-/B-(6'',7''-dimethoxy-1'',2'',3'',4''-tetrahydroisoquinolyl-1'')-ethyl/-3,4,5,6,7,8-hexahydro-(1',2':1,2-benzochinolizine) (VIII) was produced at once, which was identified as its crystalline dihydrochloride. On electrolytical reduction of (VIII) according to B. Sakurai[1] rac-C-nor-emetine (Pyman) (II) was produced.

Owing, however, to simultaneous presence of three asymm. C-atoms in the molecule of (II), the base obtained above melts over wide range, 60-80°, and its optical resolution will be the subject of further investigation.

The scheme of the present synthesis is shown in the following chart:—



1) Bull. Chem. Soc. Jap. 7 (1932), 155; 10 (1935), 311, etc.

VIII  II

Experimental

(1) Diethyl γ,γ-Dicarbethoxypimelate (IV: R = C_2H_5): This ester was already prepared by Perkin[1], but the following method of preparation is simpler. Metallic sodium (3 g, 2 mol.) was dissolved in pure alcohol (100 cc), and to this solution diethyl malonate (10.4 g, 1 mol.) was added, followed by ethyl B-bromopropionate (23.4 g, 2 mol.). The whole was refluxed for 7 hrs. and then worked up as usual. On distillation following fractions were obtained i) b.p.$_{22}$ 80-81° :2.8 g (ethyl B-bromopropionate recovered) ii) b.p.$_{10}$ 154°: 2.0 g diethyl a-carbethoxyglutarate) iii) b.p.$_{10}$ 205° : 14.6 g (diethyl γ,γ-dicarbethoxypimelate). When saponified the third fraction afforded a,$\gamma,\gamma,\varepsilon$-pentanetetracarboxylic acid of m.p. 186-187°, same with that of the authentic acid[2] given in the literature.

(2) γ,γ-Dicarbethoxypimelic acid (IV: R = H):

Method a:Alcoholic sodium ethylate solution was prepared from Na (1.2 g, 2 mol.) and pure alcohol (47 g). To this solution was added water 0.9 cc. The foregoing ester (8.7 g) was now introduced, kept standing with occasional shaking at room-temperature for 24 hrs. The sodium salt of the acid (IV: R = H) separated was dissolved by adding water, and alcohol was then removed in vac. The residue was filtered through a wet filtering paper and acidified carefully with hydrochloric acid with cooling. The solid separated (m.p. 118-121°) was purified from benzene until its m.p. remained unchanged, when it melts at 123-123.5°. Yield 6.7 g or 92% of the theoretical. ($C_{13}H_{20}O_8$ requires C 51.3, H 6.6, COOH 29.6; Found C 51.2, H 6.6, COOH 29.8).

The ester-groups on γ-carbon are more resistant towards hydrolysis than those on the ends probably due to the quaternary nature of the γ-carbon.

1) Perkin: J. Chem. Soc. 69 (1896), 1509.
2) Clemo and Tenniswood: J. Chem. Soc 1931, 2551.

Method (b): By this method the constitution of the above mentioned acid was proved. Benzyl B-bromopropionate (b.p.$_5$ 129-130°) was prepared from B-bromopropionic acid chloride and benzyl alcohol in the presence of aqueous soda solution. Di-benzyl γ,γ-dicarbethoxypimelate (IV: R = $CH_2 \cdot C_6H_5$, b.p.$_{25-3}$ 215-225°) was prepared as was described above in the case of the corresponding diethyl ester.

When the dibenzylester was reduced with hydrogen activated upon Adams-platinum-catalyst, it readily absorbed 2 mol. of hydrogen (ca. 90 cc upon 1 g ester). On working up the product, an acid melting at 123° was obtained, which m.p. was not depressed, when admixed with the acid prepared under (a). For the preparation of this acid method (a) is preferable.

(3) γ,γ-Dicarbethoxypimelic acid bis-B-homoveratrylamid (V):

The foregoing acid (3.75 g) was treated with an excess of thionylchloride. After distilling off the unchanged thionylchloride, the residue was immediately coupled with homoveratrylamin (3.1 g, 2 mol.) according to Schotten-Baumann. To the reaction solution enough sodium bicarbonate was added to destroy an excess of caustic soda, and the acid amid separated was then collected in acetic ester, washed, dried and the solvent was removed. Since the residue (4.9 g) was not induced to crystallize, it was immediately used in the next stage.

(4) Diethyl a,ε-bis-(6,7-dimethoxy-3,4-dihydroisoquinolyl-1)-pentane-γ,γ-dicarboxylate (VI): The amid (V, 4 g), pure benzene (20 cc), and freshly distilled phosphorylchloride (12 cc) were boiled gently on a steam bath for 1 hour. On cooling much petrol.-ether was added and the whole was left over night, crystalline hydrochloride of the base (VI) being then separated. This was dissolved in dil. hydrochloric acid, shaken once with ether and the aqueous layer was basified with ammonia. The base (VI) separated was extracted repeatedly with ether, washed, dried and the solvent was evaporated. The residue was crystallised from petrol.-ether added with a few drops of methanol, separating in colourless rhombic pillars of m.p. 118°. Yield 2.9 g or 77% of the theoretical ($C_{33}H_{42}O_8N_2$ requires C 66.7, H 7.1, N 4.7, M. 594; Found C 66.4, H 7.2, N 4.8, M. 585).

Picrate: Yellow leaflets from alcohol, m.p. 146-146.5°.

($C_{33}H_{42}O_8N_2 \cdot 2C_6H_3O_7N_3$ requires C 51.3, H 4.6, N 10.6; Found C 51.35, H 4.2, N 10.3).

The corresponding dicarboxylic acid, prepared by the alcaline hydrolysis of the ester, forms faint yellow pillars of d.p. 236-237°. ($C_{29}H_{34}O_8N_2$ requires C 64.7, H 6.3, N 5.2; Found C 64.9, H 6.6, N 5.0).

(5) a,ε-Bis-(6,7-dimethoxy-3,4-dihydroisoquinolyl-1)-pentane-γ-carboxylic acid (VII). The aforesaid acid (10 g) was refluxed with hydrochloric acid (75 cc of 25%) in the steam of nitrogen for 6-7

Hours, when the evolution of carbon dioxide ceased. The solution was then evaporated in vac. to dryness, and the crystalline residue was purified from alcohol-ether, forming colourless hair-like needles, melting at 160-161° under decomposition. Yield 7.5 g. ($C_{28}H_{34}O_6N_2 \cdot 2HCl \cdot 2H_2O$ requires C 55.7, H 6.6, N 4.6; Found in subst. dried at 90° for 20 hrs. C 55.8, 56.0, H 6.9, 6.4, N 4.8).

(6) 4',5'-Dimethoxy-5-keto-6-/B-(6",7"-dimethoxy-1",2",3",4"-tetrahydroisoquinolyl-1")-ethyl/-3,4,5,6,7,8-hexahydro-(1',2':1,2-benzochinolizine) (VIII): The foregoing hydrochloride (5 g) of the base (VII) in absolute alcohol absorbed smoothly 2 mol of hydrogen, activated upon Atams-catalyst. When alcohol was evaporated from the reduction solution the lactam (VIII)-hydrochloride was immediately obtained, which was purified repeatedly from absolt. alcohol: absolt. ether, forming colourless grains melting at 226-227°, which probably represent one of the racem-forms of (VIII) ($C_{28}H_{36}O_5N_2 \cdot 2HCl \cdot 2H_2O$ requires C 57.1, H 7.1, N 4.8, Cl 12.05; Found in subst. dried at 90-100° for 20 hrs. C 56.7, 57.3, H 7.5, 7.2, N 4.9, Cl 11.9).

(7) rac-C-nor-Emetine (Pyman). The aforesaid lactam-base (VIII)-hydrochloride (3 g) in 60% H_2SO_4 (ca. 70 cc) was placed in the cathode chamber and reduced at zinc-amalgam cathode (12.4 cm^2) with a current-density of 60 amp/100 cm^2 cathode. During the reduction the catholyte was mechanically stirred and the temperature was maintained at 30-35°. After five hours reduction the catholyte was made faintly alcaline with caustic soda, added then with sodium bicarbonate and extracted with acetic ester, dried and the solvent was evaporated. The residue came in colourless sandy crystals from perol.-ether, which begin sintering at 62° and melt at 78-80° with effervescence. ($C_{28}H_{38}O_4N_2 \cdot 1/2H_2O$ requires C 70.7, H 8.2, N 5.9; Found C 71.0, H 8.4, N 5.9).

The hydrochloride is hygroscopic and the determination of the melting point was impossible. The Pt-salt separates in yellow amorphous form, which decomposes at 187-189°, its recrystallization was, however, not effected from any solvents used. /$(C_{28}H_{38}O_4N_2)_2 \cdot H_2PtCl_6$ requires Pt. 14.5, Found in substance precipitated from the base of m.p. 62-80° Pt. 14.4, 14.95/.

The authors thanks are due to Miss T. Idezawa for her diligent collaboration in the present work and also to the Toshogu Tricentenary Memorial Society for research grants.

All analyses were executed by Miss K. Serikawa, Y. Takahashi and T. Sawashima.

80. Studies on the Synthesis of Emetine and its Analogues (IV)

An Improved Method for the Synthesis of rac-C-nor-Emetine Pyman*).

By Shigehiko SUGASAWA and Hajime SHIGEHARA

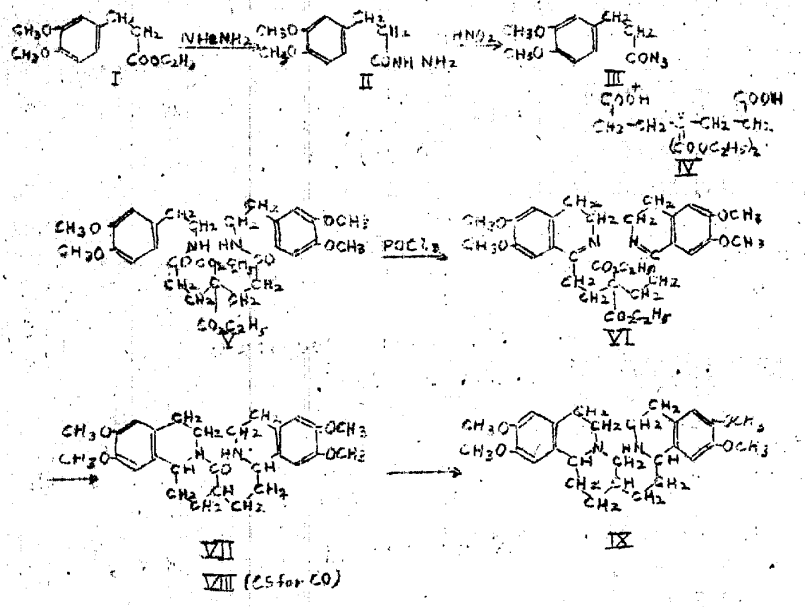
Pharmaceutical Institute, Tokyo Imperial University

(Comm. by Y. ASAHINA, M.I.A., June 12, 1944)

The synthesis of rac-C-nor-emetine-Pyman was first described by S. Sugasawa and K. Sakurai in the previous paper of this series[1]. To obtain this compound in quantity sufficient for bacteriological test by this method, we have to overcome several difficulties of which the following three items are especially to be mentioned: —

(1) The preparation of homoveratrylamine in quantity.
(2) The preparation of acid amide from this amine and γ,γ-dicarbethoxypimeric acid chloride by Schotten-Baumann-method.
(3) The last stage of the synthesis: i.e. the electrolytic reduction of the lactam.

The present synthesis proceeds according to the following scheme and we have thus succeeded in avoiding the three main difficulties in the original method.



*) S. Sugasawa: XXXIII Comm. upon "Studies on the Synthesis of Nitrogen-Ring-Compounds."
1) Proc. 17 (1941), 501.

3,4-Dimethoxycinnamic acid (100 g) in 10% aqueous caustic soda (70 cc) was reduced electrolytically at Hg-cathode, yielding the corresponding dihydro-acid in good yield (86 g). The latter was esterified (I: 70 g) and treated with hydrazine-hydrate according to Schopf[1], the hydrazide (II) being obtained in 96% yield. The crude azide (III: 54 g), prepared from (II) by the usual method, was then dissolved in pure dry benzene (700 cc) and added with γ,γ-dicarbethoxypimelic acid[2] (IV: 34 g) and the whole was then boiled gently on a steam-bath, vigorous evolution of N_2 being observed, which ceased after about 6 hrs. heating[3].

The whole was now concentrated to about 300 cc., cooled and added with pure phosphoryl chloride (160 cc) and again heated on a steam-bath for ca. 2 hrs. The reaction-product was worked up as usual, and the ester-base (VI) was obtained in fair yield (35 g, or 53% of the theoretical calculated upon the pimeric acid). It forms colourless pillars of m.p. 118° from methanol-petrolether and was proved to be identical with the specimen prepared by the former method.

From the ester-base (VI) was prepared the lactam (VII) according to the previous prescription. The latter (19 g) was now dissolved in pure benzene (300 cc) and was warmed to 40°, to which was added a mixture of K_2S (9g) and P_2S_5 (7.5 g) in small portions, and the whole was kept at 40-45° for 5 hrs. with stirring, reddish brown solution being obtained. The supernatant layer was decanted while warm and the residue was extracted twice with each 200 cc portion of benzene at 45°. From the combined solution was benzene evaporated in vac., leaving the thio-lactam (VIII) as reddish yellow viscous substance (18 g), which was not induced to crystallize and was used directly in the next stage.

The thio-lactam (18 g) was dissolved in alcohol (230 cc of 95%), acidified with conc. H_2SO_4 (25 cc), and was reduced at Pb-cathode (0.08 amp/cm^2, 20°) as usual. After 6 hrs. reduction the evolution of H_2S had ceased and colourless catholyte resulted. On working up the catholyte properly there remained colourless syrup (11 g), from which colourless amorphous solid separated by treating with benzeneligroin. It sinters from 45° and melts at 78-80° with effervescence, and seems to be identical in every respect with the specimen prepared formerly. ($C_{28}H_{38}O_4N_2 \cdot 1/2H_2O$ requires C 70.7, H 8.2; Found C 70.4, H 7.8).

It is to be emphasized that in this new method the ring-closure of the amide (V) is carried out directly in the solution, in which it is produced and thus the manipulation is greatly simplified.

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1) Schopf, Perrey and Jackh: Ann. 497 (1932), 47.
2) Sugasawa and Sakurai: loc. cit.
3) In small scale experiment the yield of the crude acid amide was about 82% of the theoretical calculated upon the pimelic acid used.

The emetine-activity of the base (IX) as hydrochloride was kindly examined by Prof. Dr. Shintaro Ishii, to whom we are greatly indebted, at the Institute for Infectious Diseases, Tokyo Imperial University, and was found to be 1/1000 as effective as the natural emetine-hydrochloride: the result is rather disappointing.

The work is being continued.

The author's thanks are due to the Toshogu Tricentenary Memorial Society for research grant. They are also indebted to Miss R. Yamaguchi for micro-analysis.

81. Studies on the Synthesis of Emetine and its Analogues (V)

Synthesis of Di-isoquinolyl-spiro-dipiperidine-Derivative*)

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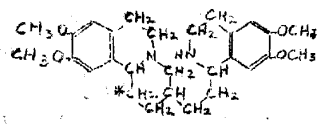
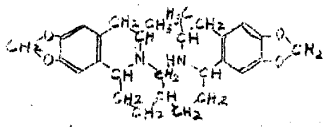
(Comm. by Y. ASAHINA, M.I.A., June 12, 1944)

In the third[1] and fourth[2] papers of this series syntheses of rac-C-nor-emetine-Pyman (I) were described, which against expectation showed only 1/1000 emetine activity[2]. In this compound the branched CH_3-group in emetine molecule, which stands on the C-atom marked with an asterisk in (I), is, therefore, substituted by H-atom. It is, however, a well-known fact, that C-CH_3-group sometimes develops a marked effect upon the physiological activity in certain compounds[3]. Since much difficulty was encountered in introducing the said CH_3-group, we now attempted to use B-(3,4-methylene dioxy-phenyl)-isopropylamine instead of homoveratrylamine in the synthesis described in the third paper, in order to reach a compound having formula (II).



I



II

On the other hand we prepared a new type of compound having di-isoquinolyl-spiro-dipiperidine-nucleus, with which synthesis the present communication deals, from the intermediate (V) for the synthesis of (II), according to the following scheme:

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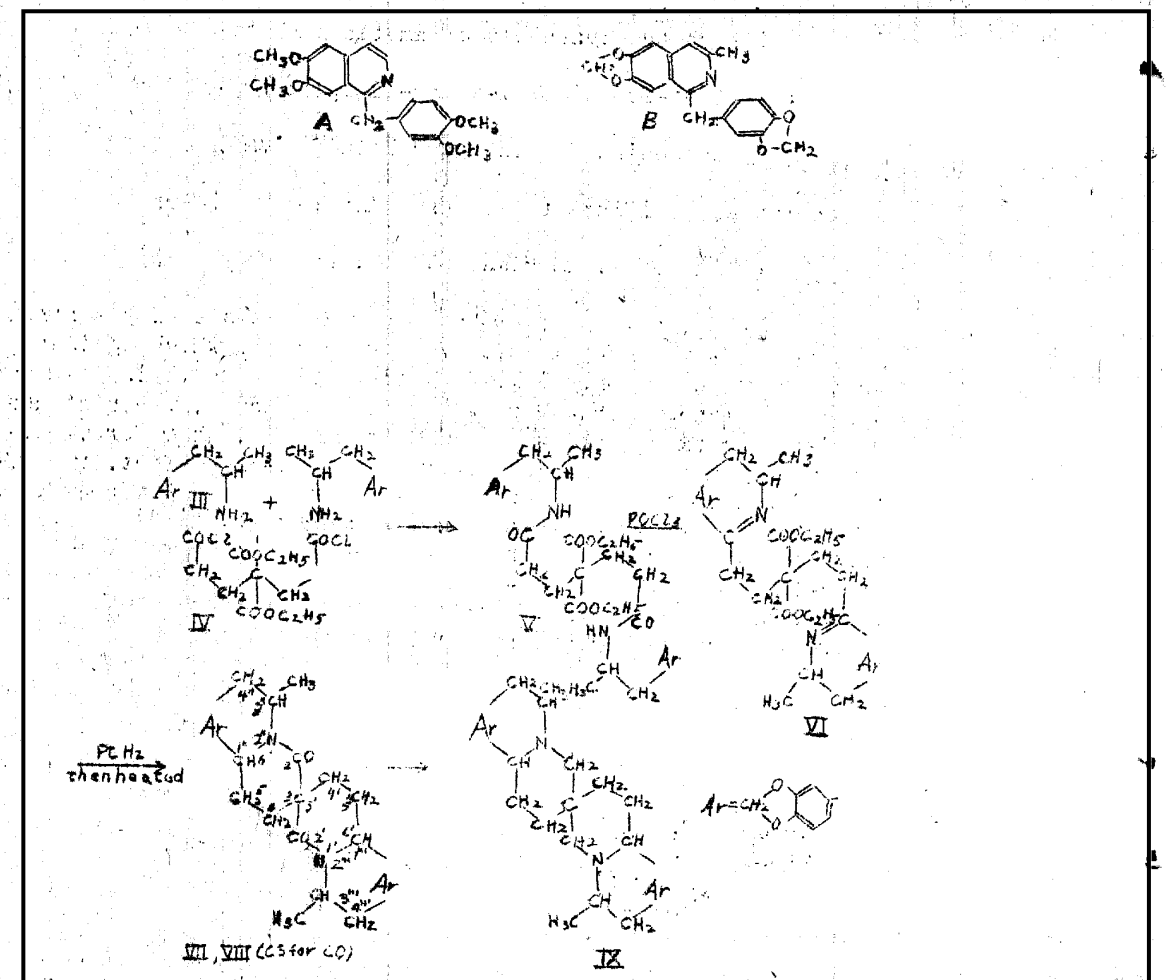
*) S. Sugasawa: XXXIV Comm. upon "Studies on the Synthesis of Nitrogen-Ring-Compounds."

1) Sugasawa and Sakurai: Proc. 17 (1941), 501.

2) Sugasawa and Shigehara: Proc. 20 (1944), 374.

3) As one of such examples papaverine (A) and eupaverine (B) are to be mentioned.



γ,γ-Dicarbethoxy-pimeric acid bis-(B-3,4-methylenedioxyphenyl-isopropylamid) (V): B-(3,4-Methylenedioxyphenyl)-isopropylamine (III; 4.7 g) was condensed with γ,γ-dicarbethoxypimeric acid chloride[1] (prepared from 5 g acid) by Schotten-Baumann-method. The amide (V) forms colourless needles of m.p. 149-150° from dioxane-petrol.-ether. Yield 8.4 g or 82% of the theoretical calculated upon the acid used. ($C_{33}H_{42}O_{10}N_2$ requires C 63.3, H 6.7, N 4.5: Found C 63.9, H 6.4, N 4.4).

1) Sugasawa and Sakurai: Proc. 17 (1941), 503.

Diethyl a,ε-Bis-(6,7-methylenedioxy-3-methyl-3,4-dihydro-isoquinolyl-1)-pentane-γ,γ-dicarboxylate (VI): The foregoing amide (8 g) in pure benzene (60 cc) was boiled with phosphoryl chloride (24 cc) and the product was worked up as usual. The base (VI) separates in faint yellow spindle-shaped crystals of m.p. 114-115° from dil. alcohol. Yield 5.5g or 73% of the theoretical. ($C_{33}H_{38}O_8N_2 \cdot 1/2H_2O$ requires C 66.1, H 6.5, N 4.6: Found C 65.8, H 6.4, N 4.6).

Dipicrate: Yellow pillars of m.p. 162-163° from dil. acetic acid. ($C_{33}H_{38}O_8N_2 \cdot 2C_6H_3O_7N_3$ requires C 51.5, H 4.2, N 10.7: Found C 51.6, H 3.8, N 10.5).

3'' ,3''' -Dimethyl-6'' ,7'' ;6''' ,7''' -bis-methylenedioxy-(1'' ,2'' : 6,1; 1''' ,2''' : 6' ,1' -bis-py-tetra-hydroisoquinolyl)-3,3' -spiro-dipiperidone-2,2' (VII): The foregoing substance(2 g)dissolved in alcohol added with a little acetic acid was reduced catalytically with hydrogen activated upon Adams-Pt., 2 mols of hydrogen being readily absorbed[2]. From the filtrate was alcohol evaporated on a steam-bath and the residue, when heated with 10% hydrochloric acid for sometime, solidified on cooling and was purified from alcohol, forming colourless needles of m.p. 269-270°. We have the dihydrochloride of compound (VII) in this substance, since it contains halogen and is devoid of property of secondary amine. The results of analyses also conform with this view. ($C_{29}H_{30}O_6N_2 \cdot 2HCl$ requires C 60.5, H 5.6, N 4.9: Found C 60.0, H 5.3, N 4.3).

The free base (VII) forms colourless needles of m.p. 74- 5° from dil. alcohol. ($C_{29}H_{30}O_6N_2 \cdot 2H_2O$ requires C 64.7, H 6.3, N 5.2: Found C 64.4, H 6.4, N 5.2).

3'' ,3''' -Dimethyl-6'' ,7'' ;6''' ,7''' -bismethylenedioxy-(1'' ,2'' : 6, 1;1''' ,2''' : 6' , 1' -bis-py-tetrahydroisoquinolyl)-3,3' -spiro-dipiperidine (IX): The above-mentioned spiro-piperidone (2 g) in pure xylene (30 cc) was warmed in oil-bath to 70°, to which was added an intimate mixture of P_2S_5 (1 g) and K_2S (1 g) in small portions during 30 min. The whole was then warmed at 95° for further 1 hr., with stirring. The supernatant layer was decanted while warm and the residue was extracted repeatedly with hot xylene. From the combined solution was xylene removed in vac., leaving the thio-lactam (VIII) as reddish brown syrup (1.8 g), which was not induced to crystallize and was used directly in the following reduction.

The thio-lactam (1.8 g) in 20% alcoholic sulphuric acid was reduced at a prepared Pb-cathode for 6 hrs. as usual (10-20°, 10 amp/100 qcm.).

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2) To our astonishment we found, that the corresponding dehydro-base, therefore having double bond between 3,4-positions in (VI), is quite resistant to catalytic hydrogenation.

The product was worked up properly and brownish yellow syrup (0.8 g) was obtained. This base (IX) showed no sign to solidify and was identified as its dipicrolonate, forming yellow needles of d.p. 237-238° from dioxane-alcohol. (Found in subst. dried at 130° for 20 hrs, in vac. C 56.5, H 5.5, N 13.6: $C_{29}H_{34}O_4N_2 \cdot 2C_{10}H_8O_5N_4 \cdot 2H_2O$ requires 56.6, H 5.2, N 13.5: Found in subst. dried at 150° for 20 hrs. in vac. C 57.4, H 4.6, N 13.5; $(C_{29}H_{34}O_4N_2 \cdot 2C_{10}H_8O_5N_4 \cdot H_2O$ requires C 57.6, H 5.1, N 13.7).

The emetine-activity of this compound (IX) as hydrogen tartarate was kindly determined by Prof. Dr. Shintaro Ishii, to whom we express our hearty thanks, at the Institute for Infectious Diseases and was found to be 1/50 as effective as emetine hydrochloride.

The syntheses of compound (II) and some of its analogues are now in progress and the results will be published in due course.

Our thanks are due to the Toshogu Tricentenary Memorial Society for research grants.

All analyses were executed by Miss H. Sugasawa, Miss R. Yamaguchi and Mr. K. Mori.

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